

## In the Literature

This section of News and Views will present updates of recent advances in the medical and scientific literature.

### Risks of Estrogen plus Progestin in Healthy Post-Menopausal Women

Jonathan Gabor, M.Sc. (OT6)

While hormone replacement therapy (HRT) is indicated for relief of menopausal symptoms and prevention of osteoporosis, its long-term use has been in vogue to prevent a range of chronic conditions, especially heart disease. Estrogen therapy alone had been the dominant form of HRT until an increased risk of endometrial cancer necessitated the addition of progestins for women with an intact uterus. Since then, evidence on the potential risks and benefits of combined estrogen/progestin has slowly accumulated and suggested that the combination acts differently than estrogen alone.

In 1993, The Women's Health Initiative (WHI) began administering the first randomized controlled trial of postmenopausal hormones. They recruited 16608 predominantly healthy postmenopausal women with an intact uterus to compare the most common HRT prescription against placebo. The primary outcome measures were coronary heart disease (CHD) and invasive breast cancer. In addition, a global statistical index, summarizing the balance of risks and benefits, was calculated to include the two primary outcomes plus stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes. The surprising results of the study are reported in the July 17 issue of the *Journal of the American Medical Association*.

After a mean of 5.2 years of follow-up, the Data and Safety Monitoring Board (DSMB) recommended stopping the trial because the test statistic for invasive breast cancer exceeded the predetermined boundary level of harm. The global index statistic indicated that risks were exceeding benefits. Several clinical outcomes suggested harm, including CHD, stroke, and pulmonary embolism. Beneficial results included decreases in colorectal cancer and hip fracture. All-cause mortality was not affected during the relatively short trial period.

The DSMB did not recommend stopping the other portion of the HRT trial, which continues to compare unopposed estrogen

with placebo in women with hysterectomies. As for the prematurely terminated estrogen/progestin trial, the results indicate that combined HRT does not meet the requirements for a viable intervention for chronic diseases and that this regime should not be initiated or continued for primary prevention of CHD.

*Writing Group for Womens Health Initiative. (2002). JAMA. 288(3): 321-333.*

### Twenty-five-year Follow-up of a Randomized Trial Comparing Radical Mastectomy, Total Mastectomy, and Total Mastectomy followed by Irradiation

Jonathan Gabor, M.Sc. (OT6)

The Halsted radical mastectomy, a removal of the entire breast tissue, pectoral muscles, and axillary lymph nodes in a single procedure, was the established and standard operation for breast cancer for most of the twentieth century. However, dissatisfaction with results, anecdotal information and emerging knowledge of tumour metastases suggested that less extensive interventions might be just as effective.

To help resolve the controversy, the National Surgical Adjuvant Breast and Bowel Project (NSABP) initiated a large clinical trial in 1971. The aims of the study were to determine whether patients with either clinically negative or clinically positive axillary nodes who received local or regional treatments other than radical mastectomy would have outcomes similar to those achieved with radical mastectomy. The 25-year findings of this trial are reported in the August 22 issue of the *New England Journal of Medicine*.

A total of 1079 women with operable breast cancer and clinically negative axillary nodes underwent either Halsted radical mastectomy, total mastectomy (removal of the entire breast tissue) without axillary node dissection but with postoperative irradiation, or total mastectomy plus axillary node dissection if their axillary nodes subsequently became pathologically positive. An additional 586 women with clinically positive axillary nodes underwent either Halsted radical mastectomy or total mastecto-

my without axillary dissection but with postoperative irradiation. Endpoints for comparison among treatment groups were disease-free survival, relapse-free survival, distant disease-free survival, and overall survival.

No significant differences were observed among the three groups of women with negative nodes or between the two groups of women with positive nodes with respect to any of the survival categories. There was no significant difference in the cumulative incidence of death unrelated to breast cancer between women who were treated with radical mastectomy and those who had a total mastectomy followed by radiation therapy, regardless of nodal status or within nodal status groups.

The findings validate earlier 10-year follow-up results showing no advantage from radical mastectomy and fail to demonstrate a significant survival advantage from removing occult positive nodes at the time of initial surgery or from radiation therapy. Although the Halsted radical mastectomy procedure is now outmoded, this pioneering trial began the trend toward less extensive surgery and led to a vast improvement in quality-of-life for women with breast cancer.

*Fisher B, Jeong JH, Anderson S, et al. (2002). N Engl J Med. 347(8):567-75.*

### **Carbon Monoxide Poisoning and the Importance of Hyperbaric Chambers**

Sergio Muraca, M.Sc. (OT6)

Carbon monoxide (CO) is a leading cause of poisoning deaths worldwide. CO is an odorless and colorless gas resulting from the incomplete combustion of organic fuels. Inhalation introduces CO into the bloodstream, where it binds to hemoglobin with an affinity that is more than 200 times stronger than that of oxygen for hemoglobin. This results in the rapid accumulation of carboxyhemoglobin (COHb), and rapid decrease in oxyhemoglobin causing tissue hypoxia. Symptoms include headaches, dizziness, fatigue, difficulty concentrating, seizures, coma, and death.

In the October 3 issue of the *New England Journal of Medicine*, an article published by Weaver et al., along with an accompanying editorial by Thom, focused on the treatment of acute CO poisoning and the importance of hyperbaric oxygen. In a double-blind, randomized trial, Weaver et al. divided 152 patients with acute CO poisoning into two groups; one group receiving three hyperbaric-oxygen sessions within 24 hours while the other group received normobaric-oxygen. The authors' main concerns were the deteriorating cognitive effects of CO-poisoning, and they performed a variety of neuropsychological tests on the day of admission, at 2 weeks, 6 weeks, 6 months and 12 months.

Six weeks after treatment, cognitive effects of CO-poisoning were identified in 25% of patients in the hyperbaric-oxygen group, which was significantly lower than the 46.1% of patients experiencing effects in the normobaric-oxygen group ( $P=0.007$ ). Furthermore, significantly fewer patients in the hyperbaric-oxygen group were still experiencing effects after 12 months [18% compared to 33% ( $P=0.04$ )].

The study was stopped prematurely based on overwhelming evidence that hyperbaric-oxygen treatments were much more effective at minimizing the neuropsychological effects of CO poisoning.

Coincidentally, just 48 hours before the release of the publication by Weaver et al., the administration at Toronto General Hospital conceded to public pressures, including the concerns of doctors, firefighters, and police, and reversed its decision to temporarily close Toronto's only hospital-based hyperbaric chamber for at least 15 months. The TGH chamber currently performs over 130 treatments a month.

*Weaver LK, Hopkins RO, Chan KJ, et al. (2002). NEJM. 347(14): 1057-67.*

*Thom SR. (2002). N Engl J Med. 347(14): 1105-6.*

### **Preventing Functional Decline in the Elderly**

Sergio Muraca, M.Sc. (OT6)

Through normal processes of aging, those of us fortunate enough to survive into our seventh decade and beyond will likely begin to experience a progressive decline in our abilities to perform activities of daily living. As we lose these abilities, we become increasingly susceptible to morbidity and mortality, resulting in hospital and nursing home admissions and use of home care resources.

It is not yet clear if functional decline is preventable in the elderly. Gill et al (2002) report their experience with 188 patients aged 75 years or older who still live at home. They evaluated each patient's ability to perform 8 activities of daily living, resulting in a cumulative disability score. Higher scores indicated greater disability. Each patient was evaluated at baseline, then blindly enrolled either into a 6-month home-based intervention program or a 6-month educational program. Participants were re-evaluated 3, 7, and 12 months from baseline. The intervention program included 16 home visits by a physical therapist, who would re-assess a patient's impairments and home environment, and go through conditioning exercises, training in the use of assistive devices, and removal of environmental hazards. The educational program included monthly visits by a health educator, who would review general practices to promote good health, including nutrition, medications, and physical activity.

Although disability scores in both groups decreased slightly

over the first 3 months, gradual increases in disability scores were observed through the remaining 9 months. However, functional decline appeared to progress significantly slower in the intervention group, suggesting that the home-based intervention program was effectively reducing the rate of functional decline, leading to an increased quality and duration of life for these patients.

In anticipation of the health care demands of our aging population, any interventions capable of preventing or minimizing functional decline in the elderly may also consequently contribute to considerable savings in public and private health care expenses.

*Gill TM, Baker DI, Gottschalk M, et al. (2002). N Engl J Med. 347(14): 1068-74.*

### **Bone Marrow-Derived Stem Cells Target Retinal Astrocytes and Can Promote or Inhibit Retinal Angiogenesis**

Susanna Fung, B.Sc. (OT6)

Vision loss in industrialized nations is associated with vascular abnormalities such as neovascularization in the choroid, arteriolar narrowing, and vascular atrophy in the eye. Blinding diseases including age-related macular degeneration, diabetic retinopathy, and inherited retinal degeneration are linked to abnormal blood vessel growth. In a recent study, Otani et al. (2002) reported the use of hematopoietic stem cells (HSCs) to selectively prevent degenerating retinal vasculature and to promote new vessel growth. HSCs injected into the vitreous gel of the mouse eye were found to target astrocytes in unvascularized areas where retinal vessels would subsequently develop. Astrocytes are thought to guide stem cells to developing blood vessels since proliferating areas of these neural glia are features of many ischemia-related ocular diseases. HSCs migrated to astrocytes in developing neonatal retinal vessels as well as in injured adult retinas and were stably incorporated into the developing vasculature. The study also showed that HSCs stabilized degenerating blood vessels and contributed to the formation of normal retinal vasculature for at least 1 month in a mutant mouse model for retinal degeneration (rd/rd). Lastly, transfection of HSCs with an anti-angiogenic protein allowed for targeted delivery to retinal vasculature at reactive astrocytes. These results suggest that stem cells can be used in a wide range of retinal vascular diseases to promote angiogenesis or to prevent abnormal vessel proliferation. Since many ocular diseases involve abnormal vessel proliferation as a response to hypoxia, the authors suggest that HSCs can be used in such cases to stabilize degenerating blood vessels and to inhibit neovascularization by delivering angiostatic proteins to the sites of angiogenesis. HSCs can also be used to stabilize degenerative vasculature without disrupting normal retinal tissue architecture.

The use of stem cells as a delivery medium for pharmacological agents holds future promise for treating a variety of ocular diseases.

*Otani et al. (2002) Nature Medicine 8(9): 1004-1010.*

### **Protein Phosphatase 1 is a Molecular Constraint on Learning and Memory**

Susanna Fung, B.Sc. (OT6)

Practice is an important determinant of learning. It allows for the formation of accurate and long-lasting memory. Time-dependent constraints are critical to learning and memory. Longer time intervals between repeated training facilitate memory retrieval. Additionally, memory gradually dissipates with time unless it is regularly retrieved and used. Genoux et al. (2002) recently reported that an enzyme called protein phosphatase 1 (PP1) is involved in suppressing memory formation and in promoting forgetting both during and after learning exercises. The authors generated mutant mice that could be induced to express an endogenous inhibitor to PP1. Massed learning, in which repeated training was crammed into a single trial, was found to produce more PP1 activity than training distributed into several sessions. When the PP1 inhibitor was activated in the mice during massed training, learning and memory was found to be enhanced to the same level as distributed training. Long-term memory formation involves a transcription factor called cyclic AMP-dependent response element binding (CREB) protein, a substrate of PP1 which becomes inactive when dephosphorylated by the enzyme. The study found that CREB activity was higher after distributed training than massed training. Expression of the PP1 inhibitor abolished differences in CREB activity between the two types of training. These results indicated that memory was improved by long intervals between learning and by blocking the PP1 inactivation of CREB, which suggest that PP1 inhibits learning by preventing gene expression. The authors also assessed long-term memory retention. They found that while PP1 inhibition solely during training did not prevent forgetting, PP1 inhibition after training maintained memory for up to 6 weeks after learning. The authors proposed that forgetting due to aging may stem from the active involvement of PP1, thus suggesting future therapeutic possibilities for the treatment of memory loss in the elderly.

*Genoux et al. (2002) Nature 418(29): 970-975.*